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ORIGINAL CONTRIBUTIONS

Heterogeneity of Melanoma Risk in Families of Melanoma Patients

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While it is recognized that relatives of melanoma patients are at increased risk for this disease, the source and extent of variation in melanoma risk between families of melanoma cases is unknown. Heterogeneity of familial melanoma risk was assessed among the families (comprising 7,666 first-degree relatives) of 1,149 cutaneous melanoma cases diagnosed in Queensland, Australia, between 1982 and 1987. The measure of familial melanoma risk was based on the number of cases of melanoma in the family in excess of those predicted from the age-, sex-, and birth cohort-specific cumulative incidences of melanoma among all relatives in the sample. Probands over-reported melanoma occurrence among their relatives, with a false positive reporting rate of 44.5% (216 false reports out of 485). Only medically verified cases among relatives were included in the analysis. There was statistically significant heterogeneity in family risk, with 53 (4.7%) of the total 1,116 unrelated families containing significantly more melanoma cases than expected considering the size of the family, and the age, sex, and birth cohort distributions of family members. In univariate analyses, members of the high-risk families were significantly more likely to have poor ability to tan, a propensity to sunburn, fair skin color, red hair, and many melanocytic nevi. When all variables were included simultaneously in a multiple logistic regression model, only the associations with tanning ability, skin color, and number of nevi remained significant. There were no significant differences overall between high-risk and other families in the sites and ages at diagnosis of melanoma, although melanomas on variably sun-exposed sites (trunk and legs) were diagnosed earlier in the high-risk families, independent of the stage at diagnosis. *Am J Epidemiol* 1994;140:961–73.

family characteristics; genetics; melanoma; nevus; risk factors; skin pigmentation

Epidemiologic evidence suggests that a family history of melanoma increases the risk for this disease, on average, by two- to threefold (1, 2). It is not known whether

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Abbreviations: CI, confidence interval; df, degrees of freedom; RR, relative risk.

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this increased risk is distributed evenly among all families of melanoma cases or whether it is due to a proportion of families at very high risk, although there appears to be considerable variation in melanoma occurrence among the families of melanoma patients. For example, a small number of families demonstrate a striking incidence of melanoma in each generation, often occurring at an early age, with a lifetime risk approaching 50 percent among the offspring of affected individuals suggestive of autosomal dominant inheritance (3–5). The majority of familial aggregations are less conspicuous, and they occur in the absence of a clear pattern of inheritance and without any clinical characteristics to distinguish them from sporadic cases. This apparent familial variation in melanoma risk may indicate either different genetic mechanisms and modes of inheritance or variation between families in the relative importance of genetic and environmental components of risk.

There is some evidence for heterogeneity of melanoma inheritance (6, 7). A melanoma susceptibility locus was recently assigned to chromosome 9p13-p22 in 11 North American kindreds (8). This finding was confirmed in 26 Australian families (9). In 1989, a susceptibility locus for the combined trait of familial melanoma and dysplastic nevus syndrome was provisionally assigned to chromosome 1p (10). This also was recently confirmed, but with evidence for statistically significant genetic heterogeneity among the 13 families tested (6). Studies of Dutch (11), Utah (12), and two sets of Australian families (13, 14) have found no evidence of linkage to chromosome 1p. While major genes such as those on chromosomes 9p and 1p may play a role in some familial aggregations, other familial clusters may be due to correlation between relatives in known melanoma risk factors, such as fair pigmentation, inability to tan, or sun exposure.

In the past, quantification of familial risk has often involved a simple count of the number of cases of disease among family members. This ignores differences in family size and the ages of family members, both of which affect the probability of disease in relatives. Here, we use a measure of familial melanoma risk based on the number of cases of melanoma in the family in excess of those predicted from the age-, sex-, and birth cohort-specific cumulative incidences of melanoma in the total sample. Thus, a high-risk family may contain more melanoma cases than expected or cases which occur at an earlier age than expected (15). The aim of this study was to assess the variation in familial melanoma risk, based on excess melanoma occurrence, among families of melanoma cases. Clinical and phenotypic characteristics of relatives from families at different levels of melanoma risk were compared to determine 1) whether there are patterns in the distribution of sites and ages at diagnosis of melanoma that might distinguish individuals in high-risk families and 2) whether increased family susceptibility may be due, at least in part, to known, measurable risk factors such as nevus density, skin type, and pigmentation.

MATERIALS AND METHODS

Study subjects

In the course of an investigation of genetic and environmental risk factors for melanoma in Queensland, Australia, we ascertained all 7,715 first incident cases of histologically confirmed invasive and in situ cutaneous melanoma diagnosed in Queensland residents between January 1, 1982 and December 31, 1987 that were reported to the Queensland Cancer Registry. An additional 148 cases were found by comparing cancer registrations for 1984 and 1987 with the records of pathology laboratories throughout Queensland. We estimate from this result that cancer registry ascertainment was approximately 95 percent complete for the study period.

Of a total 7,863 cases, current address and doctor's permission to approach the case were obtained for 6,101 (78 percent). From 4,633 cases (76 percent) who re-

sponded to a brief one-page questionnaire about family history of melanoma, and who agreed to be contacted again, 1,817 index cases (probands) were selected. The probands comprised all cases who reported one or more first-degree relatives with melanoma (n = 890) and a 25 percent random sample of those who reported no first-degree relatives with melanoma (n = 927). The study subjects for this analysis comprised all first-degree relatives (parents, siblings, and children) ascertained through a second, more detailed family history and risk factor questionnaire mailed to the probands. A total of 1,149 probands (63 percent) from 1,116 separate families returned the detailed questionnaire, and they named a total of 8,410 first-degree relatives. Responding probands included 573 (64 percent) of those who reported a positive family history and 576 (62 percent) of those who reported a negative family history. A total of 878 probands (76 percent) had histologically confirmed invasive melanoma, and 271 had melanoma in situ. Twenty-eight families in the sample were independently ascertained through two or more family members, and in these cases the oldest of these family members was nominated as the proband for the family and other probands were included as relatives. Duplicate records of relatives reported by more than one proband were removed from the data set, so that each relative was represented in the data set only once. Relatives who were adopted (n = 38), who died before one year of age (n = 23), or for whom age at death was unknown (n = 683) were excluded, leaving a total of 7,666 relatives for analysis.

Data collection

A detailed questionnaire to probands asked about standard melanoma risk factors for themselves and for their first-degree relatives, the names and addresses of these relatives, relatives' vital status, dates of birth, age at death if dead, and whether any relatives had had a melanoma diagnosed by a doctor. An abbreviated version of the questionnaire, which asked about the same risk factors but without cross-reporting on family members, was mailed to all 3,688 living relatives aged between 18 and 75 years for whom the proband provided name, date of birth, and contact address. Of these, 2,825 relatives (77 percent) responded. Relatives were asked whether they had had a melanoma or suspicious mole surgically removed, the year of diagnosis, their doctor's name and address, and for permission to view their medical records. The standard risk factors studied included pigmentary traits (natural hair color at age 21 years and unexposed skin color), sensitivity of the skin to the sun (average propensity to burn and ability to suntan), the number of painful sunburns experienced, and a qualitative rating of the number of nevi on the body (none, few, a moderate number, and many nevi, as represented in four graphical illustrations (16)). Risk factor information was obtained for 84 percent of the total group of 7,666 relatives; this included self-reports (36 percent of relatives) and surrogate reports (48 percent) provided by probands on behalf of relatives who were deceased, were unable to be contacted, or refused to participate. These percentages varied slightly for the different risk factors measured. There was reasonably good agreement between surrogate reports by probands and self-reports by relatives for all of the risk factors above except number of painful sunburns (17). Given that this item had both the highest number of missing responses by relatives (35 percent) and the lowest correlation with surrogate reports (0.23, 95 percent confidence interval (CI) 0.18–0.28), we considered it was of limited validity, and we did not include it in further analyses.

Confirmation of melanomas among relatives

Medical confirmation and dates of diagnosis were sought for all relatives reported by the probands to have had melanoma. Confirmation was sought from pathology records or, if these were not available, from

the relative's physician, hospital notes, or death certificate. Of 598 relatives reported by probands to have had melanoma, pathology or medical records could not be found for 113 (18.9 percent), usually because they had been destroyed under Australian law after a statutory 7-year period. Only two of these cases were counted as definite melanomas because the relative (or surviving spouse) gave a clear, detailed, and unequivocal description of the doctor's diagnosis and treatment of melanoma. The other 111 cases for whom records could not be found were treated as unaffected in the analysis. Of the remaining 485 cases for whom records were available, confirmation of melanoma as the diagnosis was obtained for 269 (55.5 percent). Many of the 216 (44.5 percent) false positive reports made by probands proved to be either benign nevi ($n = 50$), basal or squamous cell carcinomas ($n = 45$), cancers other than melanoma ($n = 7$), or solar keratoses ($n = 4$). An additional 81 verified cases were reported by the relatives themselves, giving a total of 352 relatives with confirmed, cutaneous melanoma. Of these, 279 relatives (79 percent) had histologically confirmed invasive melanoma, and 69 had melanoma in situ. The level of invasion was unknown in four cases.

Statistical methods

In the analyses, we used a nonparametric computer-intensive method for the detection of extra-binomial variation. In the first application of this method, Chakraborty et al. (15) presented a permutation test to evaluate excess occurrence of disease in families ascertained through an index case, taking into account the risk covariates of each family member. The number of cases of disease in a family was compared with that arising in a set of "pseudo-families" of the same size, generated by replacing each family member with a covariate-matched subject selected at random from the study sample. Extensions of this approach were presented by Fain and Goldgar (18) and Schwartz et al. (19) to test for familial heterogeneity of breast cancer risk. It is assumed in these analyses that an individual's risk of disease is homogeneous within families, conditional on the person's covariate status. While less informative than segregation analysis, which allows for heterogeneity of risk within *and* between families, such methods are useful in indicating whether particular family membership is a risk factor for disease and in identifying high-risk families for linkage analysis, and are thus an appropriate first step in the analysis of family data (15).

Quantification of familial melanoma risk. Following Fain and Goldgar (18), quantification of a family's melanoma risk was based on deviation from expected melanoma occurrence, taking into account the size of the family and the risk covariates of family members (age, sex, and birth cohort). A standardized statistic was calculated for the ith family as:

$$T_i = \frac{\sum_j O_{ij} - \sum_j E_{ij}}{\sqrt{\sum_j E_{ij}(1 - E_{ij})}}, \qquad (1)$$

where O_{ij} is melanoma status (0 or 1) and E_{ij} is the average probability of developing melanoma of the jth individual in the family, estimated as the age-, sex-, and birth cohort-specific cumulative incidence of melanoma in the total sample of first-degree relatives. A negative value of T indicates that a family contains fewer melanoma cases than would be expected in an equal-sized group of unrelated individuals drawn at random from the total sample of relatives, with the same age, sex, and birth cohort structure as the family. A positive value of T indicates that a family contains more melanoma cases than expected.

Estimation of expected probabilities of melanoma. Expected probabilities of developing melanoma among first-degree relatives of probands were estimated from the survival distribution function of the total sample of relatives via a parametric survival regression with baseline Weibull distribution, using birth cohort (eight strata:

<1910, 10-year intervals to 1969, ≥1970) and sex as covariates. This was performed using the software program PROC LIFEREG in SAS 6.07 (20). Probands were excluded from all calculations to correct for ascertainment bias. Year of birth was estimated for 903 relatives (701 parents, 188 siblings, 14 children) by assuming an average of 30 years between generations.

Test for familial heterogeneity of melanoma risk. Under the null hypothesis of homogeneous familial melanoma risk, an individual's probability of developing melanoma depends only on their age, sex, and birth cohort and not on family membership, and the expected distribution of the statistic, T, will have a mean of zero and variance of one (18). Thus, a test of the null hypothesis is equivalent to a test of whether the observed variance of T is significantly different from one.

We created an expected probability distribution for this test by generating 1,000 random permutations of the sample of 1,116 families. Each permutation was constructed by replacing each member of each family with an approximate age-, sex-, and birth cohort-matched individual selected at random from the total sample of relatives. Age was matched within 10 years for ages less than 60 years and within 2 years for ages greater than 60 years. Finer groupings were used for older ages as melanoma incidence increases rapidly after 60 years (21). Birth cohort was matched within the same groupings used for the calculation of expected probabilities, described above. Selection of relatives into the pseudo-families was independent of the relative's melanoma status. Thus, each permutation contained 1,116 pseudo-families matched to the original families by size, age group, sex, and birth cohort, and with melanoma occurrence independent of family membership.

The statistic T was calculated for each of the 1,116 families in the original sample, and its variance was computed. This was repeated for each of the 1,000 permutation samples, giving a frequency distribution of expected variances. An observed variance falling above the 95th percentile of this distribution would indicate that T had significantly greater variation in our sample than expected under the null hypothesis, and it would lead to rejection of the hypothesis of homogeneous familial risk with $\alpha = 0.05$. Given statistically significant heterogeneity of familial melanoma risk, comparison of the observed value of T for each family with those of its 1,000 size-, age-, sex-, and birth cohort-matched pseudo-families would reveal families at unusually high (or low) melanoma risk.

Adjustment for sampling scheme. Probands in our study were sampled from all melanoma cases who responded to our initial screening questionnaire using sampling fractions of 1.0 for positive family history probands and 0.25 for negative family history probands. To adjust for the different sampling fractions in the two family history strata, pseudo-families were generated by assigning relatives from negative history families a probability of selection equal to four times that of relatives from positive history families, and the variance of T was calculated as a weighted sum of the variances of negative and positive history families. Relatives from negative history families were weighted by a factor of four in the calculation of expected probabilities of melanoma.

Comparison of high-risk and non-high-risk families. To investigate associations with familial risk, we compared high-risk families with other families in terms of the distributions of known melanoma risk factors, and the sites and ages at diagnosis of melanomas among relatives. In these comparisons, families were pooled within risk groups, each relative being treated as an independent observation. Thus, significance levels and confidence intervals were slightly smaller than would otherwise have been the case. Statistical significance was initially assessed for each risk factor separately using chi-square tests for categorical variables (hair color and skin color) and ordinal variables (age group, ability to tan, propensity to sunburn, and nevus score). All variables were then included simulta-

neously in a multiple logistic regression model (22). The significance of linear trend was assessed for each factor (23). Differences between high-risk families and other families in the distribution of melanoma sites and mean ages at diagnosis were assessed using chi-square tests and 95 percent confidence intervals, respectively.

RESULTS

The sample of 7,666 relatives from 1,116 families comprised 1,604 parents, 3,367 siblings, and 2,695 children. Family sizes and the number of confirmed melanomas per family are presented in table 1. On average, melanomas were diagnosed slightly earlier in relatives (47.5 years) than in probands (50.2 years) (not significant). Among relatives, melanomas were diagnosed at significantly younger ages in later generations. Thus, the mean age at diagnosis of melanoma was 60.1 years (95 percent CI 57.0–63.2) among parents of probands, 47.3 years (95 percent CI 45.1–49.4) among siblings of probands, and 30.3 years (95 percent CI 28.4–32.3) among children of probands. To account for the different ages at censoring in each generation due to termination of the study or death from causes other than melanoma, we examined the disease-free survival distribution function for each generation using PROC LIFETEST in SAS 6.07 (20) (figure 1). Estimates were computed by the product-limit method (24). The disease-free survival functions differed significantly between generations (log-rank test, chi-square = 61.95, 2 df, $p < 0.001$); children had earlier onset of melanoma than siblings, who had earlier onset than parents.

TABLE 1. Distribution of confirmed cutaneous melanomas in 1,116 families of confirmed cutaneous melanoma cases diagnosed in Queensland, Australia, 1982–1987

No. of melanomas per family (excluding the proband)	No. of relatives per family (excluding the proband)			
	1–4	5–9	10–14	≥15
0	223	489	100	14
1	31	136	67	6
2	1	23	13	3
3	0	5	3	1
4	0	0	0	0
5	0	0	0	1
Total families	255	653	183	25

The distribution of melanoma sites in probands varied according to the sex of the proband (chi-square = 80.57, 3 df, $p < 0.001$). Men had relatively more melanomas on the trunk (49.6 percent) and face (14.4 percent) and fewer melanomas on the arms (20.8 percent) and legs (15.2 percent) than did women (25.8, 12.3, 29.4, and 32.5 percent, respectively). There was a similar pattern among relatives with melanoma, although the sex-specific differences did not reach statistical significance. There was no relation between melanoma sites among relatives and sites in the related probands, either overall (chi-square = 9.87, 9 df, $p = 0.361$) (table 2) or when the analysis was restricted to male relatives of male probands or to female relatives of female probands.

Heterogeneity of familial melanoma risk among families of melanoma cases

The statistic T had a variance in our sample of 2.26 (see figure 2), coinciding with the 99.9th percentile of its expected distribution generated from the 1,000 permutation samples. This implies that if the null hypothesis were true, a variance of the magnitude that we observed would be expected to occur by chance only 0.1 percent of the time. We therefore rejected the null hypothesis, and we concluded that there was statistically significant familial heterogeneity in melanoma risk among the 1,116 families in our sample ($p = 0.001$). A similar, significant result was obtained when we restricted the analysis to the families of probands with invasive melanoma only and, within these families, when we counted as affected only those relatives with confirmed invasive melanoma. Results were also unchanged when we excluded from the analysis the 111 relatives with unconfirmed, positive reports.

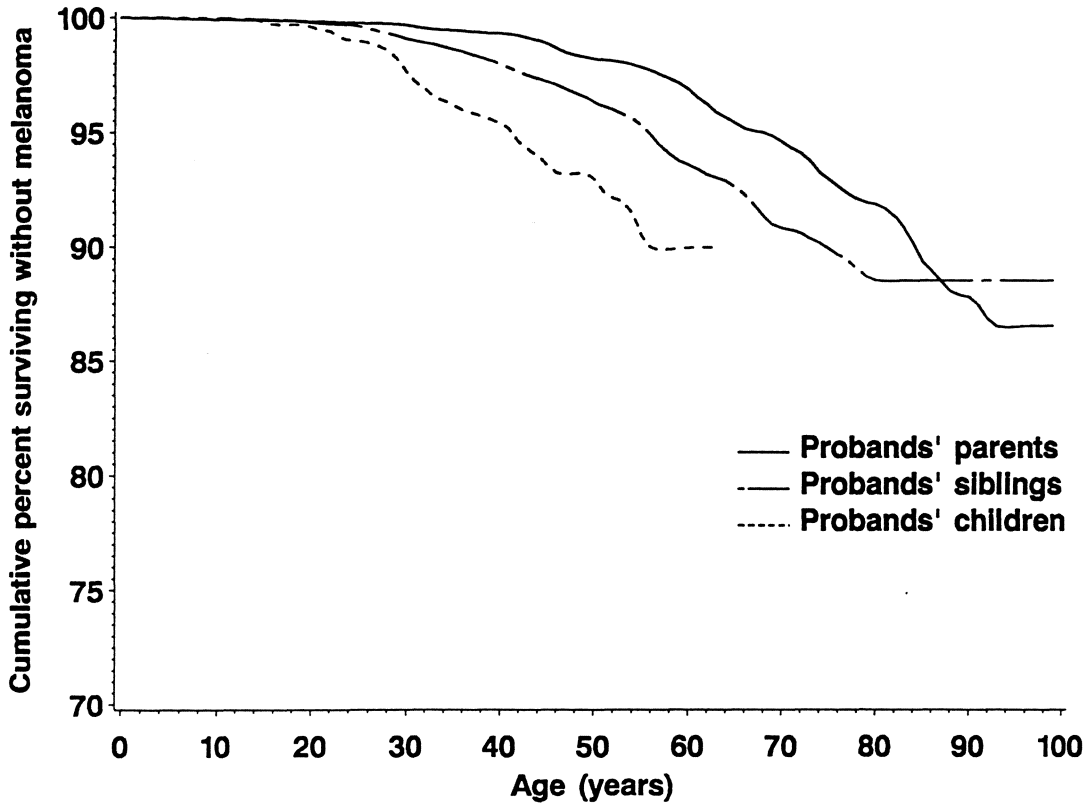

FIGURE 1. Cumulative melanoma-free survival among first-degree relatives of confirmed cutaneous melanoma cases (probands) diagnosed in Queensland, Australia, 1982–1987, according to the relative's relationship to the proband.

TABLE 2. Site of melanomas in first-degree relatives of confirmed cutaneous melanoma cases diagnosed in Queensland, Australia, 1982–1987, according to site in the related proband

Site of melanoma in relative	Site of melanoma in proband							
	Face		Arms		Trunk		Legs	
	No.	%	No.	%	No.	%	No.	%
Face	7	(20.0)	9	(13.4)	11	(11.1)	4	(5.3)
Arms	7	(20.0)	18	(26.9)	24	(24.2)	18	(24.0)
Trunk	8	(22.9)	23	(34.3)	39	(39.4)	27	(36.0)
Legs	13	(37.1)	17	(25.4)	25	(25.3)	26	(34.7)
Total*	35	(100.0)	67	(100.0)	99	(100.0)	75	(100.0)

* There were a total of 352 affected relatives, but either the relative's or the proband's site of melanoma was unknown for 76 of these relatives.

To determine whether heterogeneity was due to a subgroup of families at higher or lower risk, we ranked the T of each family against those of its 1,000 matched pseudo-families. Using a two-tailed 5 percent significance test, a family with a percentile rank of 97.5 or above (or 2.5 or below) has significantly higher (or lower) cumulative incidence of melanoma than would be expected in an equal sized group of unrelated individuals selected at random from the total sample of relatives, matched on age, sex, and birth cohort. Fifty-three families (4.7 percent),

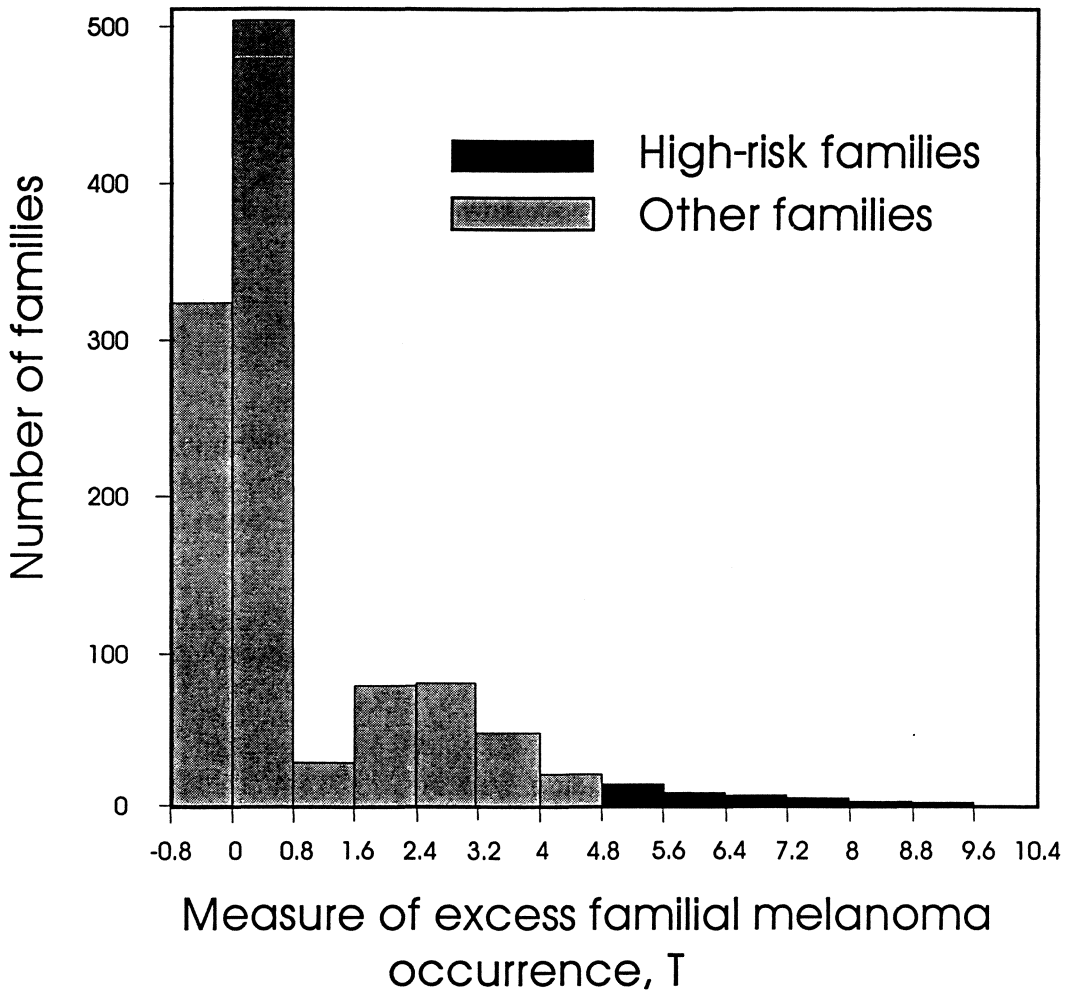

FIGURE 2. Distribution of *T*, a measure of excess familial melanoma occurrence (see text), in 1,116 families of confirmed cutaneous melanoma cases (50 percent reporting a positive family history) diagnosed in Queensland, Australia, 1982–1987. Self-reported negative history families were weighted by a factor of four to reflect sampling fractions. A negative (positive) value of *T* indicates that a family contains fewer (more) melanoma cases than would be expected in an equal sized group of unrelated individuals drawn at random from the total sample of relatives, with the same age, sex, and birth cohort structure as the family.

comprising 411 relatives (102 with confirmed cutaneous melanoma), had ranks of 97.5 or above, and according to our a priori definition, were at significantly higher familial melanoma risk (i.e., contained significantly more melanoma cases than expected). No families were at significantly lower risk. This was because the mean number of expected cases per family in our sample was 0.15, and pseudo-families with no affected relatives always made up at least the lowest 13 percent of the sampling distribution of *T*.

Associations between high familial melanoma risk and characteristics of family members

To determine whether apparent susceptibility to melanoma in some families might be associated with a higher prevalence of known melanoma risk factors, families were arbitrarily subdivided into four groups according to their percentile rank of *T* (<50, 50–94.9, 95–97.4, and 97.5 percentile or above). All but two of the 828 families (74 percent) who were ranked below the 50th percentile compared with their

matched pseudo-families contained no relatives with confirmed melanoma, while all 288 families (26 percent) who were ranked at or above the 50th percentile contained at least one affected relative in addition to the proband.

The three lowest percentile groups appeared to have very similar risk factor distributions, and log-linear models incorporating all phenotypic variables listed in table 3 revealed that these groups could be combined without significant loss of fit (likelihood ratio test, chi-square = 72.73, 73 df, $p = 0.487$). We therefore present summary results comparing relatives in the 53 high-risk families with relatives in the

TABLE 3. Demographic characteristics, family size, and melanoma risk factors among first-degree relatives of confirmed cutaneous melanoma cases diagnosed in Queensland, Australia, 1982–1987, according to familial melanoma risk*

Characteristic	Relatives in 1,063 non-high-risk families (n = 7,255)	Relatives in 53 high-risk families (n = 411)	Adjusted relative risk†	95% confidence interval	p value for trend
Mean no. of relatives per family	6.8	7.8			
No. of relatives with confirmed melanoma	250 (3.4)‡	102 (24.8)			
Relatives' ages (years)					
<40	2,816 (38.8)	191 (46.5)	1.0		
40–70	3,079 (42.4)	165 (40.1)	0.85	0.66–1.08	
>70	1,360 (18.7)	55 (13.4)	0.81	0.56–1.18	0.39
Relatives' melanoma risk factors					
Ability to tan					
Good	1,084 (17.9)	45 (11.5)	1.0		
Moderate	2,708 (44.8)	160 (40.8)	1.33	0.88–1.99	
Slight	1,653 (27.3)	116 (29.6)	1.44	0.89–2.35	
Poor	603 (10.0)	71 (18.1)	2.15	1.15–4.01	0.006
Unknown	1,207	19			
Propensity to burn					
Never burns	426 (7.0)	22 (5.7)	1.0		
Sometimes burns	3,090 (51.0)	161 (41.8)	0.55	0.33–0.94	
Usually burns	1,730 (28.6)	124 (32.2)	0.57	0.31–1.03	
Always burns	808 (13.3)	78 (20.3)	0.69	0.34–1.39	0.81
Unknown	1,201	26			
Hair color at age 21					
Black	625 (9.6)	36 (9.1)	1.0		
Light/dark brown	3,966 (60.9)	218 (54.9)	0.66	0.44–0.99	
Fair/blonde	1,391 (21.3)	78 (19.6)	0.62	0.39–0.98	
Light/dark red	534 (8.2)	65 (16.4)	1.26	0.77–2.07	0.10
Unknown	739	14			
Skin color					
Olive	602 (9.2)	15 (3.8)	1.0		
Medium	2,243 (34.3)	110 (27.8)	2.22	1.19–4.11	
Fair	3,693 (56.5)	271 (68.4)	2.62	1.39–4.94	0.07
Unknown	717	15			
Nos. of nevi					
No nevi	1,053 (19.7)	43 (11.9)	1.0		
Few nevi	2,988 (55.8)	205 (56.6)	1.90	1.32–2.72	
Moderate number	1,094 (20.4)	88 (24.3)	2.14	1.43–3.21	
Many nevi	217 (4.1)	26 (7.2)	2.94	1.71–5.06	<0.001
Unknown	1,903	49			

* Based on deviation from expected melanoma occurrence; see text.

† Relative risks compare high-risk families with other families, and are adjusted for age group, sex, and all phenotypic variables in the table.

‡ Numbers in parentheses are percentages.

other 1,063 families. Relatives from high-risk families were significantly younger than relatives from other families, and correspondingly, a higher proportion were born in 1950 or later. In univariate analyses, there were significant differences between the two groups in the distributions of all risk factors examined, with a larger proportion of relatives from high-risk families falling into the highest risk category for each factor. Thus, comparatively more relatives from high-risk families had poor ability to tan, high propensity to sunburn, red hair, fair skin, and many melanocytic nevi. This was also true when comparisons were restricted to the 352 relatives with melanoma, although differences failed to reach statistical significance, presumably because of the reduced statistical power of the smaller sample. When all variables were included simultaneously in a multiple logistic regression model (table 3), only ability to tan, skin color, and nevus score remained significantly associated with high familial melanoma risk, with relative risks of 2.15 (95 percent CI 1.15–4.01) for poor versus good ability to tan, 2.62 (95 percent CI 1.39–4.94) for fair versus olive skin, and 2.94 (95 percent CI 1.71–5.06) for having many nevi versus no nevi. Tests for positive trend were significant for ability to tan ($p = 0.006$) and nevus score ($p < 0.001$). Results were similar when we excluded from the logistic regression analysis the 111 relatives with unconfirmed positive reports.

There was no significant difference between the high-risk families and the other families either in the sites at which melanoma was diagnosed or in the mean age at diagnosis of melanoma in probands and in relatives (table 4). These results did not change when the analysis was restricted to probands and relatives with invasive melanoma only. There were differences in regard to relatives' site-specific ages at diagnosis, with melanomas in high-risk families that occurred somewhat later on chronically sun-exposed sites (face and arms), and 6.6 years earlier on variably sun-exposed sites (trunk and legs). This difference just failed to reach statistical significance at the 5 percent level. There was a higher proportion of in situ lesions on the trunk and legs in high-risk families compared with other families (22 percent vs. 16 percent). However, this did not explain the earlier age at diagnosis, as both types of lesions were diagnosed earlier in the high-risk group (46.8 vs. 51.0 years for in situ lesions on the trunk and legs, and 39.9 vs. 47.5 years for invasive lesions).

DISCUSSION

Significant heterogeneity in familial melanoma risk was detected among the families of melanoma cases drawn from a

TABLE 4. Site and age at diagnosis of melanoma in first-degree relatives of confirmed cutaneous melanoma cases diagnosed in Queensland, Australia, 1982–1987, according to familial melanoma risk *

	Non-high-risk families (n = 1,063)				High-risk families (n = 53)			
	No.	%	Mean age at diagnosis (years)	95% confidence interval	No.	%	Mean age at diagnosis (years)	95% confidence interval
Probands	1,063		50.3	49.4–51.2	53		48.3	44.8–51.8
Relatives with melanoma	250	(100.0)	47.7	45.5–49.8	102	(100.0)	47.1	43.7–50.6
Chronically sun-exposed sites (face, arms)	73	(29.2)	47.3	43.3–51.2	28	(27.5)	54.5	47.7–61.3
Variably sun-exposed sites (trunk, legs)	132	(52.8)	48.0	45.0–51.0	55	(53.9)	41.4	37.3–45.6
Unknown site	45	(18.0)	47.4	42.5–52.4	19	(18.6)	52.8	44.9–60.7

* Based on deviation from expected melanoma occurrence; see text.

population-based cancer registry in Queensland, Australia. Melanoma is one of the most common malignancies in Queensland (21), and some family clusters are therefore likely to occur by chance, particularly in large kindreds. The method used here evaluates excess cumulative incidence of melanoma in families, beyond that expected given the size of the family, and its age, sex, and birth cohort structure. By incorporating individual risk covariates of family members, this technique provides a more precise and thus more powerful alternative to the traditional epidemiologic approach to familial risk assessment, often based on a simple count of the number of affected relatives, or the prevalence of positive family history among cases and controls (1, 2, 25).

Schwartz et al. (19) have used a similar analysis to examine heterogeneity of familial breast cancer risk. In their study, expected probabilities of breast cancer were calculated using recent age-, sex-, and race-specific population incidence rates. Here, age- and sex-specific incidence rates among relatives were between 1.5 and 3 times higher than corresponding population incidence rates in Queensland for 1979–1980 (21), consistent with epidemiologic evidence that a family history of melanoma increases melanoma risk by two- to three-fold (1, 2). Rather than use population rates in the present analysis, we estimated expected probabilities of melanoma from the observed cumulative incidences in our sample. The observation that melanoma is diagnosed at earlier ages in succeeding generations is consistent with the increasing age-specific incidence of melanoma in Queensland over recent decades (21). To account for this, and for possible differences in diagnostic and surveillance practices and in the quality of family history information between cohorts (18), expected melanoma probabilities were conditioned on birth cohort, in addition to age and sex.

Melanomas in relatives were included in the analysis only if we were able to obtain medical record confirmation, or, in two cases, after discussion with the relative or their spouse. We attribute the surprisingly high rate of false positive reporting by probands, namely 45 percent, to an apparent lack of understanding in the Australian community of the term "melanoma" (26). As our data show, melanoma seems to be confused with the far more common malignancies which are also excised from the skin (basal and squamous cell carcinomas), and with benign nevi which are also frequently excised, the reason often being to exclude melanoma. While we are unaware of other reports of the validity of self-reported family history of melanoma, these results indicate that verification is probably necessary in all studies utilizing self-reported family melanoma histories. Misclassification may have resulted in underestimation of familial melanoma risk in the past (1, 2, 16). Of course, a proportion of the 111 reported melanomas for which we were unable to obtain medical records may have been true cases. Including these would have increased the power of the analysis and may have provided stronger evidence for familial heterogeneity, given that we found similar rates of misclassification by probands from high-risk and other families.

Heterogeneity in family risk is caused by familial variation in disease risk factors (19), including genetic susceptibility, phenotypic risk factors, shared environmental exposures, of which solar radiation is recognized as the most important for melanoma (27), or a combination of these. While the present analysis cannot indicate the causes of a familial excess in melanoma occurrence, this excess is unlikely to be due simply to similar environmental exposures among relatives. If we can assume, for example, that the correlation between the sun exposures of first-degree relatives is not larger than that reported between sun exposures from 10 to 20 years of age for same-sex dizygotic twins in Britain (0.35) (28), then this factor would have to be very strongly associated with melanoma, with a relative risk approaching 100 or more, to produce a doubling of risk among relatives of affected probands (29). In Australian populations, a relative risk for melanoma of

5.3 in the highest category of sun exposure is the strongest association yet reported for this risk factor (30), whether measured as total accumulated sun exposure or recent, usual, or recreational exposure. Even if measurement error had caused the true association to be underestimated by half, it would be necessary to postulate unreasonably high correlation between relatives' sun exposures for this factor alone to have produced the considerable excess melanoma occurrence seen among high-risk families in our sample (29, 31). It is likely, then, that inherited genetic susceptibility plays some role in familial correlation for melanoma.

Members of high-risk families were significantly more likely to have high-risk phenotypes, suggesting that, insofar as there is an inherited predisposition to melanoma, it may be partly accounted for by known, measurable risk factors which are themselves genetically determined, including propensity to develop nevi, skin color, and ability to tan. It is also possible that these phenotypic risk factors may raise the penetrance of a major susceptibility gene. An examination of differences among families in their joint distributions of sun exposure and of phenotypic traits that might modify the carcinogenic effect of solar radiation would be a first step in quantifying this contribution to familial risk. These considerations highlight the importance in family studies of recording as much information as possible on relatives' risk factors, to enable the analysis of environmental, genetic, and phenotypic causes of increased familial risk. When self-reports are not available, surrogate reports by probands of their relatives' melanoma risk factors can provide a reasonable alternative (17).

The observation that melanomas on the trunk and legs, both in situ and invasive, were diagnosed at earlier ages in high-risk families is consistent with a recent hypothesis (32) that melanocytes on less sun-exposed sites such as the trunk may be more susceptible to malignant change than those on the face. That is, in individuals at highest genetic risk, genetic predisposition to melanoma may be greater on the trunk and legs, and thus melanomas here occur at an earlier age than on the face because a smaller dose of solar radiation is required to precipitate malignant change.

It is apparent from the present analysis that when the background melanoma incidence rate is high, as in Queensland (21), a cluster of affected relatives may occur by chance without necessarily implying unusual family susceptibility. The definition of high familial risk used here was based on an arbitrary statistical cutpoint, and it has no biologic significance. It does not exclude the possibility that lower ranked familial aggregations have some genetic, or other familial, basis. Nevertheless, this method allows the identification of a subgroup of families who are most likely to be at higher melanoma risk than other families, and so has the potential to simplify the study of the genetic and environmental causes of familial aggregation of melanoma. The search for familial melanoma genes, for example, may benefit from the exclusion from gene linkage studies of familial aggregations that are consistent with chance occurrence.

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